VIVAGLOBIN - human immune globulin g solution
CSL Behring LLC

Manufactured by:
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US License No. 1765
Distributed by:
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R_x only

DESCRIPTION

Vivaglobin®, Immune Globulin Subcutaneous (Human) is a pasteurized, polyvalent human normal immunoglobulin for subcutaneous infusion. Vivaglobin® is manufactured from large pools of human plasma by cold alcohol fractionation and is not chemically altered or enzymatically degraded.

Vivaglobin® is supplied as a sterile liquid to be administered by the subcutaneous route. Vivaglobin® is a 16% (160 mg/mL) protein solution, with a content of at least 96% immunoglobulin G (IgG). The distribution of IgG subclasses is similar to that present in normal human plasma. Vivaglobin® contains 2.25% glycine, 0.3% sodium chloride, and water for injection, U.S.P. The pH of Vivaglobin® is 6.4 to 7.2. Vivaglobin® contains no preservative.

All plasma used in the manufacture of Vivaglobin® is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2) as well as FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be nonreactive (negative). For hepatitis B virus (HBV), an investigational NAT procedure is used and the plasma found to be negative. However, the significance of a negative result has not been established. In addition, the plasma has been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 (B19). Only plasma that passed virus-screening is used for production and the limit for B19 in the fractionation pool is set not to exceed 10^4 IU of B19 DNA per mL.

The manufacturing procedure for Vivaglobin® includes multiple processing steps that reduce the risk of virus transmission. The virus reduction capacity of two steps was evaluated in a series of *in vitro* spiking experiments; the steps were ethanol - fatty alcohol / pH precipitation and pasteurization in aqueous solution at 60°C for 10 hours. Total mean cumulative virus reductions ranged from 9.0 to ≥ 14.1 $\log_{10}$ as shown in Table 1.

Table 1: Mean Virus Reduction Factors

Virus Studied:	**Ethanol - Fatty Alcohol / pH Precipitation [$\log_{10}$]**	**Pasteurization [$\log_{10}$]**	**Total Cumulative [$\log_{10}$]**
Enveloped Viruses			
HIV-1	≥ 6.2	≥ 6.5	≥ 12.7
BVDV	≥ 5.3	≥ 8.7	≥ 14.0
WNV	≥ 4.4	≥ 9.3	≥ 13.7
PRV	≥ 6.2	≥ 7.9	≥ 14.1
Non-enveloped Viruses			
PEV	≥ 6.7	3.7	≥ 10.4
CPV	6.7	2.3*	9.0

HIV-1: Human immunodeficiency virus type 1, model for HIV types 1 and 2
BVDV: Bovine viral diarrhea virus, model for HCV and WNV
WNV: West Nile virus
PRV: Pseudorabies virus, model for large enveloped DNA viruses (e.g., herpes virus)
PEV: Porcine enterovirus, model for HAV (in an immunoglobulin product)
CPV: Canine parvovirus, model for parvovirus B19
*****Reduction of parvovirus B19 (evaluated using porcine IgG) by pasteurization was ≥ 3.5 $\log_{10}$.

CLINICAL PHARMACOLOGY

Vivaglobin®, Immune Globulin Subcutaneous (Human) supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents.

Vivaglobin® is to be administered by injection into the subcutaneous tissue. Subcutaneous administration of immune globulin decreases bioavailability compared to intravenous administration.[1] The bioavailability of Vivaglobin® is approximately 73% compared to immune globulin intravenous (IGIV). Various factors, such as the site of administration and IgG catabolism, can affect absorption.[1,2] With Vivaglobin® administration, peak serum IgG levels are lower than those achieved with IGIV. Subcutaneous administration results in relatively stable steady-state serum IgG levels when administered on a weekly basis.[2,3] This serum IgG profile is representative of that seen in a normal population.

The pharmacokinetics (PK) of Vivaglobin® was evaluated in the PK phase of a pivotal 12-month clinical study conducted in the United States and Canada in subjects with primary immune deficiency (PID) (see **CLINICAL STUDIES**). Subjects who were previously treated with IGIV were switched over to weekly Vivaglobin® subcutaneous treatment and, after a 3-month wash-in/wash-out period, doses were individually adjusted to provide an IgG systemic exposure (area under the curve; AUC) that was not inferior to the AUC of the previous weekly-equivalent IGIV dose. For the 19 per-protocol subjects completing the wash-in/wash-out period, the average Vivaglobin® dose adjustment was 137% (range: 103 to 192%) of the previous weekly-equivalent IGIV dose. Following 10 to 12 weeks of treatment with Vivaglobin® at this adjusted dose, the final steady-state AUC determinations were made. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for Vivaglobin® versus IGIV treatment was 94.5% (range: 71.4 to 110.1%) with a lower 95% confidence limit of 89.8% for the per-protocol population (n = 17). Table 2 summarizes additional pharmacokinetic parameters for this study including dosing and serum IgG peak and trough levels following treatment with IGIV and Vivaglobin®.

Table 2: Summary of Additional Pharmacokinetic Parameters – US and Canada PK Sub-study – Per-protocol Subjects

	IGIV	**Vivaglobin®**
Number of Subjects	**17**	**17**
Dose*		
Mean	120 mg/kg	165 mg/kg
Range	55 – 243 mg/kg	63 – 319 mg/kg
IgG peak levels		
Mean	1735 mg/dL	1163 mg/dL
Range	1110 – 3230 mg/dL	743 – 2240 mg/dL
IgG trough levels		
Mean	883 mg/dL	1064 mg/dL
Range	430 – 1600 mg/dL	547 – 2140 mg/dL

*****For IGIV: weekly-equivalent dose

A non-IND 6-month clinical study was conducted in Europe and Brazil in 60 subjects with PID. After the subjects had reached steady state with weekly Vivaglobin® administration, peak serum IgG levels were observed after a mean of 2.5 days (range 0 to 7 days) in 41 subjects.

In contrast to serum IgG levels observed with monthly IGIV treatment (rapid peaks followed by a slow decline), the serum IgG levels in subjects receiving weekly subcutaneous Vivaglobin® therapy were relatively stable in both studies.

CLINICAL STUDIES

The pivotal open-label, prospective, multicenter clinical study conducted in the United States and Canada evaluated the pharmacokinetics, efficacy, safety and tolerability of Vivaglobin®, Immune Globulin Subcutaneous (Human) in adult and pediatric subjects with primary immune deficiency (PID). In this study, 65 adult and pediatric PID subjects previously treated monthly with IGIV were switched to weekly subcutaneous administrations of Vivaglobin® for 12 months. The per-protocol efficacy analysis included 51 subjects. Subjects received a weekly mean Vivaglobin® dose of 158 mg/kg body weight (range: 34 to 352 mg/kg), which was 136% (range: 99 to 188%) of their previous weekly-equivalent IGIV dose.

The annual rate of serious bacterial infections (defined as bacterial pneumonia, meningitis, sepsis, osteomyelitis, and visceral abscesses), the primary endpoint, was 0.04 infections per subject per year (one-sided upper 99% confidence interval: 0.14) for the per-protocol set (n = 51). Pneumonia was reported in two subjects. The annual rate of any infections, a secondary endpoint, was 4.4 infections per subject per year.

The IgG subclass levels observed in this study were consistent with a physiologic distribution pattern (mean values) IgG_1: 703 mg/dL, IgG_2: 278 mg/dL, IgG_3: 36 mg/dL, and IgG_4: 30 mg/dL.

Table 3 summarizes the dosing and annual rate of infections for the efficacy phase of this study.

Table 3: Dose and Annual Rate of Infections with Vivaglobin® – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects (Efficacy)	**51**
Vivaglobin® Dose	
Mean % Previous IGIV Dose (range):	136% (99 – 188%)
Mean:	158 mg/kg b.w.
Range:	34 – 352 mg/kg b.w.
Annual Rate of Serious Bacterial Infections:	0.04 infections/subject year
Annual Rate of Any Infections:	4.4 infections /subject year

b.w.: body weight

Table 4 provides a summary of missed school or work and hospitalization due to infection, which were secondary endpoints.

Table 4: Summary of Secondary Efficacy Endpoints – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects	**51**
Total Number of Subject Days	18,949
Total Number of Days Missed School/Work Due to Infection (%)	192 (1.0%)
Annual Rate Missed School/Work Due to Infection (days/subject year)	3.70
Total Number of Days Hospitalized Due to Infection (%)	12 (< 0.1%)
Annual Rate of Hospitalization (days/subject year)	0.23

In a non-IND clinical study of Vivaglobin® conducted in Europe and Brazil, 60 adult and pediatric subjects with PID were switched to weekly subcutaneous administration of Vivaglobin® for six months. Forty-nine (49) subjects had been on IGIV and 11 subjects had been treated long-term with another brand of Immune Globulin Subcutaneous (Human) replacement therapy before entering the study. The forty-seven (47) per-protocol subjects received a weekly mean Vivaglobin® dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% (range: 81 to 146%) of their previous immune globulin treatment. The annualized rates of serious bacterial infections (0.04 infections/subject year, one-sided upper 99% confidence interval: 0.21) and any infections (4.3 infections/subject year) were similar to those reported in the study conducted in the US and Canada.

INDICATIONS AND USAGE

Vivaglobin®, Immune Globulin Subcutaneous (Human) is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS

As with all immune globulin products, Vivaglobin®, Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS

Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin®, Immune Globulin Subcutaneous (Human).
If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have been possibly transmitted by this product

should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.
During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS

General

Administer Vivaglobin®, Immune Globulin Subcutaneous (Human) subcutaneously. **Do not administer this product intravenously.** The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests

After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions

Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin®, Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C

Animal reproduction studies have not been conducted with Vivaglobin®, Immune Globulin Subcutaneous (Human). It is also not known whether Vivaglobin® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Vivaglobin® should be given to a pregnant woman only if clearly needed.

Pediatric Use

Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use

The clinical study of Vivaglobin®, Immune Globulin Subcutaneous (Human) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In clinical studies, administration of Vivaglobin®, Immune Globulin Subcutaneous (Human) has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see **CONTRAINDICATIONS**).
Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject Irrespective of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)

Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*****Excluding infections
†Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion Irrespective of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events (Rate†)**
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)‡

*****Excluding infections
†Rate = number of reactions/infusion
‡Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*****Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate†)**
Adverse Events at the Injection Site	1787 (49%)

Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

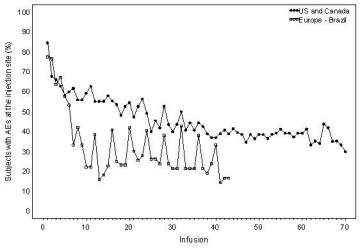
*****Excluding infections
†Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions

Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

DOSAGE AND ADMINISTRATION

Vivaglobin®, Immune Globulin Subcutaneous (Human) contains no preservative. Therefore, discard unused product immediately after use.

Vivaglobin® must not be mixed with other products.

Vivaglobin® is to be injected subcutaneously, preferentially in the abdomen, thighs, upper arms, and/or lateral hip.
DO NOT INJECT INTO A BLOOD VESSEL.

Dosage

All subjects who received Vivaglobin® in the clinical trials had previously been treated with immune globulin. It is recommended that the patient start treatment with Vivaglobin® one week after receiving a regularly scheduled IGIV infusion.

The initial weekly Vivaglobin® dose can be calculated by multiplying the previous IGIV dose by 1.37, then dividing this dose into weekly doses based on the patient's previous IGIV treatment interval; for example, if IGIV was administered every three weeks, divide by 3. This dose of Vivaglobin® will provide a systemic IgG exposure (AUC) comparable to that of the previous IGIV treatment. Weekly administration of this dose will lead to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared to monthly IGIV treatment (see Table 2 for trough levels).

The recommended weekly dose of Vivaglobin® is 100 to 200 mg/kg body weight administered subcutaneously. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. As there can be differences in the half-life of IgG among patients with primary immune deficiencies, the dose and dosing interval of immunoglobulin therapy may vary.

Doses And Associated IgG Levels

The minimum serum concentration of IgG necessary for protection against infections has not been established in randomized and controlled clinical studies. However, based on clinical experience, a target serum IgG trough level (i.e., prior to the next infusion) of at least 500 mg/dL has been proposed in the literature for IGIV therapy.[4]

Serum IgG levels can be sampled at any time during routine weekly treatment. Subjects on Vivaglobin® therapy maintained relatively constant IgG levels, rather than the peak and trough pattern observed with monthly IGIV therapy.

Administration

DO NOT INJECT INTRAVENOUSLY.

In the clinical study with Vivaglobin®, a volume of 15 mL per injection site at a rate of 20 mL per hour per site was not exceeded. Doses over 15 mL were divided and infused into several sites using an infusion pump. Multiple simultaneous injections were enabled by administration tubing and Y-site connection tubing (CADD-Legacy® pumps were used in the study conducted in the US and Canada). Injection sites were at least two inches apart.

The following areas were used for subcutaneous injection of Vivaglobin®: abdomen, thighs, upper arms, and/or lateral hip. The actual point of injection was changed with each weekly administration.

Instructions for Administration

Prior to use, allow the solution to reach ambient room temperature. Vivaglobin® should be inspected visually for discoloration and particulate matter prior to administration. DO NOT SHAKE. The appearance of Vivaglobin® can vary from colorless to light brown. Do not use if the solution is cloudy or has particulates. Check the product expiration date on the vial. Do not use beyond the expiration date.

1. Use aseptic technique when preparing and administering Vivaglobin® for injection.
2. Remove the protective cap from the vial to expose the central portion of the rubber stopper.
3. Wipe the rubber stopper with alcohol and allow to dry.
4. Using a sterile syringe and needle, prepare to withdraw Vivaglobin® by first injecting air into the vial that is equivalent to the amount of Vivaglobin® to be withdrawn. Then withdraw the desired volume of Vivaglobin®. If multiple vials are required to achieve the desired dose, repeat this step. (Fig. 2)
5. Follow the manufacturer's instructions for filling the pump reservoir and preparing the pump, administration tubing and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with Vivaglobin®.
6. Select the number and location of injection sites depending on the volume of the total dose. Note: In clinical studies with Vivaglobin®, a volume of 15 mL per injection site was not exceeded. (Fig. 3)
7. Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least two inches apart. (Fig. 4)
8. Grasp the skin between two fingers and insert the needle into the subcutaneous tissue. (Fig. 5)
9. Vivaglobin® must **not** be injected into a blood vessel. After each needle is inserted into the tissue, test to make sure that a blood vessel has not been accidentally accessed. This must be done prior to starting the infusion. To do this, attach a sterile syringe to the end of the primed administration tubing, gently pull back on the syringe plunger and look to see if any blood is flowing back into the administration tubing. If you see any blood, remove and discard the needle and administration tubing. Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site. (Fig. 6)
10. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
11. Infuse Vivaglobin® following the manufacturer's instructions for the pump. (Fig. 7)

12. Remove the peel-off label with the product lot number and expiration date from the Vivaglobin® vial and use this to complete the patient record.

Fig. 2

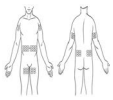


Fig. 3

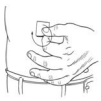


Fig. 4

Fig. 5

Fig. 6

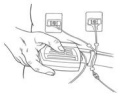


Fig. 7

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

Home Treatment
If the physician believes that home administration is appropriate, the physician or health professional should provide the patient with instructions on subcutaneous infusion for home treatment. This should include the type of equipment to be used along with its maintenance, proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip), maintenance of a treatment diary, and measures to be taken in case of adverse reactions.

HOW SUPPLIED

Vivaglobin®, Immune Globulin Subcutaneous (Human) is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

NDC 0053-7596-01	3 mL carton
NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL carton
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL carton
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE

Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin®, Immune Globulin Subcutaneous (Human) is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

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3. Data on file.

4. Roifmann CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobuli naemia and chronic lung disease. *Lancet* 1987;1(8451):1075-7.

Revised: April 2009
Part number A3085 G46 (20740A)

CSL Behring

Vivaglobin®
Immune Globulin Subcutaneous (Human)
[Pronounced VEE-vah-glow-bin]

Information for patients

This summary contains important information you need to know about Vivaglobin® for treating primary immunodeficiency (also known by its abbreviation, "PID"). *Please read it carefully before you start your treatment.* This summary is based on information given to your doctor but does not include all available information about Vivaglobin®. The summary is not meant to take the place of your doctor's instructions and should be used only after you have received instructions from your doctor. You should discuss any questions about treatment with Vivaglobin® with your doctor.

What is Vivaglobin®?

Vivaglobin® is a highly purified product, called an immune globulin, made from human plasma. Vivaglobin® contains the antibody immunoglobulin G (IgG), which is found in the blood of healthy individuals to help combat germs, such as bacteria and viruses. Because it helps the body rid itself of these bacteria and viruses, IgG is important in helping the body fight infection.

Vivaglobin® also contains the following inactive ingredients: 2.25% glycine, 0.3% sodium chloride, and water for injection.

What is Vivaglobin® used for?

Vivaglobin® is a prescription medication used to treat patients with primary immunodeficiency.

Vivaglobin® is supplied as a sterile liquid in single-use vials and is given by infusion subcutaneously (under the skin). **Do not administer Vivaglobin® into a blood vessel (vein or artery) as there is no safety information in patients supporting this route of administration.**

For treatment to be effective, you must carefully follow your doctor's instructions regarding your dose and treatment schedule for Vivaglobin®.

How does Vivaglobin® work?

Vivaglobin® treats primary immunodeficiency, a condition in which a person's natural defense system—or immune system—does not function properly.

Normally, our immune system helps protect us against infections by recognizing potentially harmful bacteria and viruses that enter our body every day. In response, the immune system produces special proteins called antibodies that fight these foreign invaders. However, when our immune system is not working properly, it is unable to produce these valuable antibodies, leaving us more vulnerable to infection and illness.

Vivaglobin® is known as antibody replacement therapy, because it replaces the missing and much-needed IgG antibodies in people who have low levels of this infection-fighting protein. By replacing these important antibodies, Vivaglobin® helps make people with PID better able to avoid infections and fight them when they do occur.

Who should <u>NOT</u> take Vivaglobin®?

People who have a history of allergic reactions to immunoglobulins or have a condition known as selective IgA deficiency should not use Vivaglobin®. Tell your doctor if you have ever had an allergic reaction due to either of these conditions. If a serious allergic reaction occurs at any time, stop the Vivaglobin® treatment and contact your doctor or an emergency medical professional immediately.

Because clinical studies with pregnant women have not been conducted, if you are pregnant or think you may be pregnant, discuss with your doctor whether Vivaglobin® is clearly needed. Please also consult your doctor about the use of this product if you are a nursing mother.

What are possible side effects of Vivaglobin®?

In clinical studies, Vivaglobin® has been shown to be safe and well tolerated in both adults and children. As with any medication, side effects may accompany treatment.

The frequency of side effects was based on a review of over 5,900 injections given during the clinical trials. The most frequently reported side effect was injection site reaction, which generally consisted of mild or moderate swelling, redness, and itching at the site of injection. In clinical trials, these reactions tended to decrease substantially over time. Please contact your healthcare provider if you would like more information on managing these reactions.

Other side effects may include:

- Headache
- Gastrointestinal disorder
- Fever
- Nausea
- Sore throat
- Rash

- Allergic reaction
- Increased cough
- Pain
- Diarrhea

If you are concerned about these or any other side effects, please talk to your healthcare provider.

What additional important information do I need to know about Vivaglobin®?

Vivaglobin® is made from the plasma portion of human blood. All plasma used to produce Vivaglobin® is collected in a manner that meets or exceeds U.S. Food and Drug Administration requirements. For your safety, we maintain stringent controls over plasma collection and processing every step of the way. Because Vivaglobin® is made from plasma, as are all immune globulins, the risk of transmitting infectious agents, including viruses, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent, cannot be completely eliminated. However, the risk that Vivaglobin® will transmit diseases is reduced by carefully screening plasma donors for prior exposure to certain viruses and by testing plasma for evidence of potentially harmful viruses. Only plasma that passed virus-screening is used for production of Vivaglobin®.

During the manufacture of Vivaglobin®, specific viral clearance methods further decrease the chance of disease transmission. The main virus reduction step of the Vivaglobin® manufacturing process is a pasteurization technique, which involves heating the product at 140°F (60°C) for 10 hours. Additional purification procedures used in the manufacture of Vivaglobin® further reduce the risk of disease. As with all products manufactured from human plasma, however, the risk of transmitting infectious agents cannot completely be eliminated. However, during clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

If you believe that you have contracted an infection that was possibly transmitted by Vivaglobin®, you should report this to your doctor or healthcare provider.

What medications should I avoid while taking Vivaglobin®?

Vivaglobin® can impair the efficacy of certain virus vaccines, such as measles, mumps and rubella (also known by its abbreviation "MMR"). Inform the immunizing physician of recent treatment with Vivaglobin® so appropriate precautions can be taken.

Other products must not be mixed with the Vivaglobin® solution.

How do I store Vivaglobin®?

Vivaglobin® is supplied in single-use vials. It contains no preservatives, so any unused portion should be discarded immediately after use. When stored in the refrigerator at 36° to 46°F (2° to 8°C) Vivaglobin® can be used until the expiration date on its label. Do not use after the expiration date. *Do not freeze Vivaglobin®*. Keep the vial in its box during storage.

Keep Vivaglobin® and all other medications out of the reach of children.

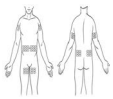
How do I use Vivaglobin®?

Vivaglobin® is infused subcutaneously (under the skin). Do not administer it into a blood vessel (vein or artery).
Your doctor will determine the appropriate dose for your treatment.

Your doctor or healthcare provider will teach you the proper techniques for administering Vivaglobin®. **Only after such instruction should you follow the instructions below.**

Preparing for your treatment

The following areas are recommended for subcutaneous infusion of Vivaglobin®:



- Abdomen
- Thighs
- Upper arms
- Hip

For proper selection of infusion site, please consult your doctor or healthcare provider.

Instructions for administration

The following instructions are intended only as a guide. Before administering Vivaglobin®, you should be under the care of a doctor and should have received proper training on proper preparation and administration from a licensed healthcare provider.

Fig. 1

1. Prior to use, allow the vial(s) of Vivaglobin® to reach room temperature, 68° to 77°F (20° to 25°C). On a clean, flat surface, such as a table, assemble all the supplies you will need for your treatment, including Vivaglobin® vials, treatment diary/ logbook, an infusion pump, administration tubing, subcutaneous needle or catheter, Y-site connection tubing (if needed), alcohol wipes, antiseptic skin preps, syringe(s), needle(s), gauze or transparent dressing, tape and a sharps disposal container. Your healthcare provider can help you to identify a complete list of supplies. Discuss with your healthcare provider whether you should use gloves when preparing Vivaglobin® for infusion. (Fig. 1)

2. There are several different types of ambulatory infusion pumps that may be used to administer Vivaglobin®. Your healthcare provider will help you to determine which type of pump is appropriate for you. Follow the pump manufacturer's instructions for preparing the infusion pump and priming the administration tubing. Set the rate of infusion on the pump as instructed by your healthcare provider.

Fig. 2

3. Before preparing Vivaglobin® for infusion, thoroughly wash and dry your hands. (Fig. 2)

Fig. 3

4. Before each infusion, be sure to visually inspect each vial of Vivaglobin® for discoloration and for particles in the solution by gently swirling each vial (do **not** shake the vial). Vivaglobin® should be a clear solution that can vary from colorless to light brown. If the solution in a vial is cloudy or contains particles, or if the protective cap is missing, do not use it. Check the expiration date on each vial of Vivaglobin®. Do not use beyond the expiration date. (Fig. 3)

Fig. 4

Fig. 5

5. Remove the protective cap from each vial of Vivaglobin®. Next, cleanse the top of each vial stopper with an alcohol wipe, and allow the top of the vial to dry. (Figs. 4 and 5)

Fig. 6

6. Using aseptic technique as instructed by your healthcare provider, attach a needle to the syringe tip. (Fig. 6)

Fig. 7

7. Pulling back on the syringe plunger, draw back a volume of air into the syringe that is equal to the volume of Vivaglobin® that will be withdrawn. With the Vivaglobin® vial placed on a flat surface, insert the needle into the center of the vial stopper. Then inject the air into the vial. Next, leaving the syringe and needle in the vial, carefully invert the vial as shown in the illustration. Withdraw the Vivaglobin® solution into the syringe and remove the filled syringe from the vial. Remove the needle from the syringe filled with Vivaglobin® and discard the needle into a sharps disposal container. Repeat this step if multiple vials are required to achieve the prescribed dose of Vivaglobin®. (Fig. 7)

Fig. 8

8. Follow manufacturer's instructions for filling the infusion pump reservoir and priming the administration tubing and needle/catheter. "Priming" the administration tubing refers to the removal of the air from the tubing and needle/catheter that will be used to infuse Vivaglobin®. Priming may also be done by connecting the syringe filled with Vivaglobin® to the administration tubing and gently pushing on the syringe plunger to fill the tubing with Vivaglobin® until a drop is seen exiting the needle/catheter. (Fig. 8)

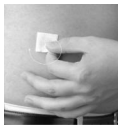


Fig. 9

9. Select an appropriate infusion site(s), depending on the amount required for your total Vivaglobin® dose and the instructions of your healthcare provider. Cleanse the site(s) with antiseptic skin prep(s) beginning in the center of the site and working outward in a circular motion. Allow site(s) to dry before proceeding to the next step. If your healthcare provider recommends that you administer Vivaglobin® using multiple sites, ensure that each site is at least two inches apart. (The maximum recommended infusion volume per infusion site is 15 mL). (Fig. 9)

Fig. 10

10. Using two fingers, grasp the skin around the infusion site. As instructed by your healthcare provider, insert the needle directly into the subcutaneous tissue and **not** into a blood vessel. (Fig. 10)

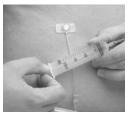


Fig. 11

11. After each needle is inserted into the tissue, you must test to make sure that a blood vessel has not been accidentally entered. This must be done prior to starting your infusion. To do this, attach a sterile syringe to the end of the primed administration tubing, and gently pull back on the syringe plunger. Look to see if any blood is flowing back into the administration tubing. If you see any blood, remove and discard the needle and administration tubing. Then, repeat steps 8–11 using a new needle, administration tubing and a new infusion site. (Fig. 11)

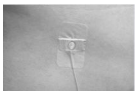


Fig. 12

12. Secure the needle by applying sterile gauze or transparent dressing over the site and tape in place. (Fig. 12)

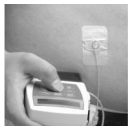


Fig. 13

13. Secure the administration tubing to the infusion pump following the manufacturer's instructions and turn on the pump. (Fig. 13)

Fig. 14

14. Once the infusion is complete, turn off the infusion pump. Remove the needle(s) from the infusion site(s) and discard any unused solution and administration equipment in accordance with biohazard procedures as recommended by your healthcare provider. Follow the manufacturer's instructions regarding care of the infusion pump after each use. (Fig. 14)

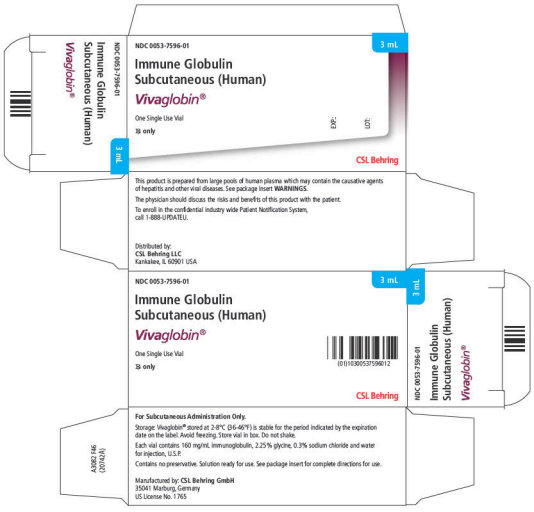
Fig. 15

15. On each Vivaglobin® vial, you will find a peel-off label with the product lot number and expiration date. Record the time, date, and exact dose of your infusion, then remove the labels and affix them to your treatment diary/logbook. Take this record of your treatment with you whenever you visit your physician. (Fig. 15)

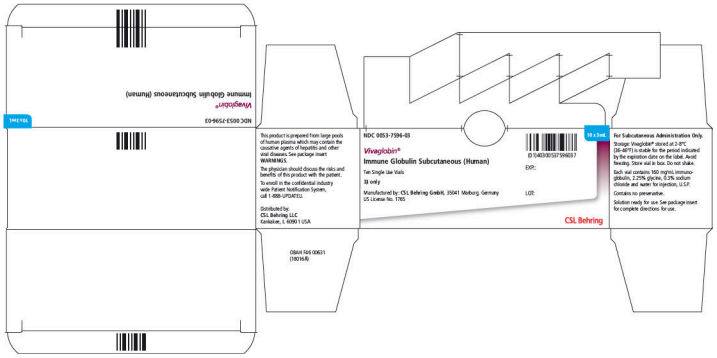
These instructions are intended to serve as a guide for people who have already been instructed by a healthcare professional on the proper method of preparing and administering Vivaglobin®. If you have not received such training, please consult your healthcare provider before attempting to administer Vivaglobin®. If you experience any problems or need more information regarding your subcutaneous treatment, contact your healthcare provider.

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765
Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA
Revised: April 2009
Part number A3084 G46 (20926A)

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 3 ML VIAL CARTON
NDC 0053-7596-01
3 mL
Immune Globulin
Subcutaneous (Human)
***Viva**globin*®
One Single Use Vial
Rx only
EXP.:
LOT:
CSL Behring

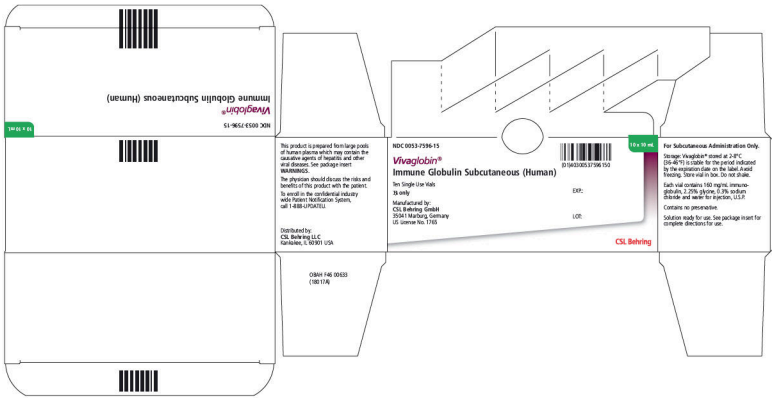


PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 10 × 3 ML
NDC 0053-7596-03
10 × 3 mL
***Viva**globin*®
Immune Globulin Subcutaneous (Human)
Ten Single Use Vials
Rx only
Manufactured by: **CSL Behring GmbH,** 35041 Marburg, Germany
US License No. 1765
EXP.:
LOT:
CSL Behring



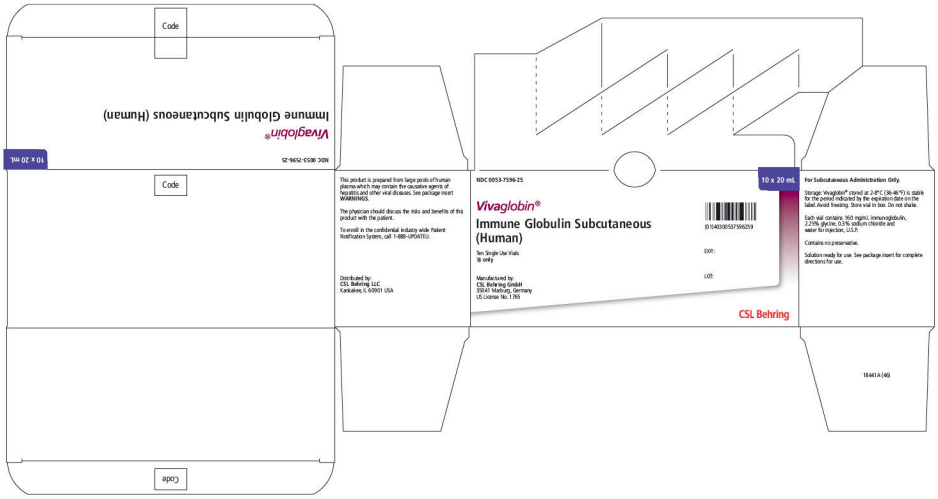
PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 10 ML
NDC 0053-7596-10
10 mL
Immune Globulin
Subcutaneous (Human)
Viva*globin*®
One Single Use Vial
Rx only
EXP.:
LOT:
CSL Behring

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 10 × 10 ML
NDC 0053-7596-15
10 × 10 mL
Viva*globin*®
Immune Globulin Subcutaneous (Human)
Ten Single Use Vials
Rx only
Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765
EXP.:
LOT:
CSL Behring



PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 20 ML
NDC 0053-7596-20
20 mL
Immune Globulin
Subcutaneous (Human)
Viva*globin*®
One Single Use Vial
Rx only
EXP.:
LOT:
CSL Behring

PACKAGE LABEL - PRINCIPAL DISPLAY PANEL - 10 × 20 ML
NDC 0053-7596-25
10 × 20 mL
Viva*globin*®
Immune Globulin Subcutaneous (Human)
Ten Single Use Vials
Rx only
Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765
EXP.:
LOT:
CSL Behring



Revised: 10/2009

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